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(54) Title: USE OF FORMOTEROL IN MEDICAMENT FOR INFLAMMATION/ALLERGY IN UPPER AIRWAYS

(57) **Abstract**

The invention provides the use of an active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate of formoterol, or a solvate of such a salt in the manufacture of a medicament for use in the treatment of an inflammatory and/or allergic condition in the upper airways of a human being.

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USE OF FORMOTEROL IN MEDICAMENT FOR INFLAMMATION/ALLERGY IN UPPER AIRWAYS

FIELD OF THE INVENTION

The invention provides the use of formoterol in the treatment of inflammatory and allergic conditions in the upper airways of human beings.

BACKGROUND OF THE INVENTION

Inflammatory and allergic conditions in the upper airways include conditions such as rhinitis, sinusitis and nasal polyps. Conditions such as these are conventionally treated by corticosteroid nasal sprays. The problem with using corticosteroids to treat these conditions is that it takes some time before they take effect.

The use of a beta-2-adrenostimulant, fenoterol, to treat seasonal allergic rhinitis has been investigated. It was found that it had an insignificant effect upon nasal hypersecretion and nasal blockage caused by the rhinitis (Borum et al, Allergy 42, (1987), pp. 141-145).

US-A-4,975,466 to Ciba-Geigy relates to pharmaceutical preparations containing formoterol or one of its pharmaceutically acceptable salts, especially its semifumarate, for treatment of inflammatory skin diseases. The preparations are mainly used for topical, i.e. dermal, application, to the skin and/or mucous membrane, since formoterol is said to have a very pronounced antiphlogistic (dermally phlogistatic) topically anti-inflammatory, action. More specifically, the preparations are intended for external use on the outer skin, including the conjunctiva of the eyeball, the lips and the genital and anal region. There is no information about use of formoterol or preparations thereof for alleviating inflammatory and/or allergic conditions in the upper airways.

C. Advenier et al, Br. J. Pharmacol., 105 (1995), pp. 792-798 relates to the effects of the β 2 -adrenoceptor agonists, salbutamol and formoterol, on the increase of micro-vascular permeability induced by histamine or bradykinin in guinea-pig airways. In the nasal mucosa, only salbutamol in doses of 30 µg/kg showed a significant inhibitory effect against histamine whereas formoterol 10 µg/kg significantly increased the effects of histamine in a dramatic manner. Therefore, Advenier et al strongly indicates that use of formoterol in the treatment of inflammatory and/or allergic conditions in the upper airways should be avoided.

Accordingly there is a need for an effective treatment which has a faster onset time and a long duration.

SUMMARY OF THE INVENTION

The present invention is directed to the use of formoterol, or pharmaceutically acceptable salts or solvates thereof for manufacturing medicaments suitable for use in the treatment of an inflammatory and/or allergic condition in the upper airways of a human being.

According to a preferred embodiment of the invention, the active ingredient is formoterol fumarate dihydrate.

DETAILED DESCRIPTION OF THE INVENTION

According to the invention there is provided the use of an active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate of formoterol, or a solvate of such a salt in the manufacture of a medicament for use in the treatment of an inflammatory and/or allergic condition in the upper airways of a human being.

According to the invention there is also provided a method of treating a patient suffering from an inflammatory and/or allergic condition in the upper airways which comprises

administering to the patient a therapeutically effective amount of the active ingredient, wherein the patient is a human being.

According to the invention there is further provided a pharmaceutical composition comprising the active ingredient in association with one or more pharmaceutically acceptable diluent, carrier or additive, which composition is for use in the treatment of an inflammatory and/or allergic condition in the upper airways of human beings.

Formoterol is an adrenoreceptor agonist which selectively stimulates β_2-receptors, with the formula (N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methyl-ethyl]-amino]-ethyl]-phenyl]-formamide. It has surprisingly been found to be effective in the treatment of inflammatory and allergic conditions in the upper airways of human beings. Inhaled formoterol has the advantage that it both acts rapidly, usually within minutes, and exerts a prolonged effect of up to 12 hours.

Suitable physiologically acceptable salts of formoterol include acid addition salts derived from inorganic and organic acids, for example the chloride, bromide, sulfate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulfonate, methanesulfonate, ascorbate, acetate, succinate, lactate, glutarate, gluconate, tricarballylate, hydroxynaphthalene-carboxylate or oleate salts or solvates thereof. The active ingredient is preferably formoterol fumarate, especially the dihydrate.

Formoterol, pharmaceutically acceptable salts and solvates of formoterol, and solvates of such salts can be prepared by the methods described in US-A-5,434,304 to Astra and DE-A-2,305,092 to Yamanouchi.

The preferred daily dose of the active ingredient is from 5 to 250 nmol (preferably from 15 to 120 nmol). When the active ingredient is formoterol fumarate dihydrate the preferred daily dose is from 3 to 96 µg, more preferably from 3 to 48 µg and most preferably from 3

to 24 μg per day. Examples of suitable unit doses include 3, 4.5, 6, 9 and 12 μg of formoterol fumarate dihydrate.

The invention provides a new and surprisingly effective treatment for inflammatory and/or allergic conditions in the upper airways of a human being. The conditions treatable by the invention are preferably in the nose and paranasal sinus. They include

- seasonal allergic rhinitis which is pollinosis caused by pollens from ragweed, birch, grass, cedar or other plants
- perennial allergic rhinitis caused by e.g. dust mites (Dermatophagoides pteronyssinus and D. farinae), cockroaches and mammals such as cats, dogs and horses
- perennial non-allergic rhinitis
- nasal polyps, as well as prevention of post surgical nasal polyps
- chronic sinusitis
- recurrent sinusitis and
- hypertrophic adenoids.

Preferably the active ingredient is used in admixture with one or more pharmaceutically acceptable additives, diluents or carriers, preferably in an amount of from 50 μg to 25 mg per dose, more preferably in an amount of from 50 μg to 10 mg, most preferably in an amount of from 100 to 4000 μg. Examples of suitable diluents or carriers include lactose, dextran, mannitol and glucose. Preferably lactose is used, especially as the monohydrate.

The active ingredient used in the invention is preferably in the form of a dry powder, more preferably a finely divided, e.g. a micronized, dry powder, e.g. having a mass median diameter of less than 10 μm, for example from 1 to 5 μm, most preferably an agglomerated micronized dry powder. Preferably at least 90% of the powder particles have a size below 15 μm. As an alternative to agglomeration the finely divided active ingredients may be in the form of an ordered mixture with one or more pharmaceutically acceptable additives, diluents or carriers. An ordered mixture is the combination of a finely divided active ingredient with coarse particles of a pharmaceutically acceptable additive, diluent and/or carrier.

The ingredients used in the invention can be obtained in these preferred forms using methods known to those skilled in the art.

The invention will be illustrated by the following examples which are not intended to limit the scope of the invention.

EXAMPLES

EXAMPLE 1

10 parts of formoterol fumarate dihydrate was mixed with 990 parts of lactose monohydrate. The blend was micronized using a high pressure air jet mill and then conditioned using the process of EP-A-717616. The mixture was then spheronised using the process of EP-A-721331, divided into parts, each of which were filled into the storage compartment of a Turbuhaler™ fitted with a dosing disc such that it administered, when activated, a unit dose of 6 µg.

Example 2

20 parts of formoterol fumarate dihydrate was mixed with 980 parts of lactose monohydrate. The blend was micronized using a high pressure air jet mill and then conditioned using the process of EP-A-717616. The mixture was then spheronized using the process of EP-A-721331, divided into parts, each of which were filled into the storage compartment of a Turbuhaler™ fitted with a dosing disc such that it administered, when activated, a unit dose of 12 µg.

CLAIMS

1. Use of an active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate of formoterol, or a solvate of such a salt in the manufacture of a medicament for use in the treatment of an inflammatory and/or allergic condition in the upper airways of a human being.

2. Use according to claim 1, wherein the active ingredient is formoterol fumarate dihydrate.

3. Use according to claim 1 or 2, wherein the inflammatory and/or allergic condition is selected from the group consisting of seasonal allergic rhinitis, perennial allergic rhinitis, perennial non-allergic rhinitis, nasal polyps, chronic sinusitis, recurrent sinusitis and hypertrophic adenoids.

4. Use according to any previous claim, wherein the active ingredient is a finely divided dry powder, preferably an agglomerated micronized dry powder.

5. Use according to claim 4, wherein the finely divided dry powder has a mass median diameter of less than 10 μm, preferably in the range of from 1 to 5 μm.

6. Use according to any previous claim, wherein the daily dose of the active ingredient is from 5 to 250 nmol, preferably from 15 to 120 nmol.

7. A method of treating a human patient suffering from an inflammatory and/or allergic condition in the upper airways, which comprises administering to the human patient a therapeutically effective amount of an active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate of formoterol, or a solvate of such a salt.

8. The method according to claim 7, wherein the active ingredient is formoterol fumarate dihydrate.

9. The method according to claim 7 or 8, wherein the inflammatory and/or allergic condition is selected from the group consisting of seasonal allergic rhinitis, perennial allergic rhinitis, perennial non-allergic rhinitis, nasal polyps, chronic sinusitis, recurrent sinusitis and hypertrophic adenoids.

10. A pharmaceutical composition comprising an active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate of formoterol, or a solvate of such a salt in admixture with a pharmaceutically acceptable diluent, carrier and/or additive, which composition is for use in the treatment of an inflammatory and/or allergic condition in the upper airways of a human being.

11. The pharmaceutical composition according to claim 10, wherein the active ingredient is formoterol fumarate dihydrate.

12. The pharmaceutical composition according to any one of claims 10 or 11, wherein the active ingredient is a finely divided dry powder, preferably an agglomeratedmicronized dry powder or an ordered mixture.

13. The pharmaceutical composition according to claim 12, wherein the finely divided dry powder has a mass median diameter of less than 10 μm, preferably in the range of from 1 to 5 μm.

14. The pharmaceutical composition according to any one of claims 10 to 13, wherein the dose of active ingredient in admixture with a pharmaceutically acceptable diluent, carrier and/or additive, lies in the range of from 50 μg to 25 mg, preferably from 100 μg to 4 mg.

15. The pharmaceutical composition according to any one of claims 10 to 14, wherein the inflammatory and/or allergic condition is selected from the group consisting of seasonal allergic rhinitis, perennial allergic rhinitis, perennial non-allergic rhinitis, nasal polyps, chronic sinusitis, recurrent sinusitis and hypertrophic adenoids.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/02278

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/165
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	British Journal of Pharmacology, Volume 116, 1995, Stella R. O'Donnell et al, "The effects of formoterol on plasma exudation produced by a localized acute inflammatory response to bradykinin in the tracheal mucosa of rats in vivo", page 1571 - page 1576, page 1575, column 2, lines 14-33	1-15
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X	Journal of applied physiology, Volume 77, 1994, J.J. Bowden et al, "Inhibition of neutrophil and eosinophil adhesion to venules of rat trachea by Beta2-adrenergic agonist formoterol", page 397 - page 405, page 404, lines 11-17	1-15
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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 March 1999	01 -04- 1999
Name and mailing address of the ISA Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. + 46 8 666 02 86	Authorized officer Patrick Andersson Telephone No. + 46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/02278

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Br. J. Pharmacol, Volume 105, 1992, C. Advenier et al, "Formoterol and salbutamol inhibit bradykinin- and histamine-induced airway microvascular leakage in guinea-pig", page 792 - page 798, see especially page 794, column 2, lines 29-35	1-15
X	US 5668110 A (RONALD W. BARRETT ET AL), 16 Sept 1997 (16.09.97), column 22, line 23 - line 30; column 24, line 1 - line 13; column 26, line 9 - line 21, claim 15	1-15
X	WO 9619198 A1 (ASTRA AKTIEBOLAG), 27 June 1996 (27.06.96), page 6, line 1 - line 9, claim 19	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/02278

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 7,8,9
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 7,8,9 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body /Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/03/99

International application No.
PCT/SE 98/02278

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5668110 A	16/09/97	NONE	
WO 9619198 A1	27/06/96	AU 4359396 A	10/07/96
		BR 9510510 A	07/07/98
		CA 2206782 A	27/06/96
		CN 1170356 A	14/01/98
		CZ 9701947 A	15/10/97
		EP 0806940 A	19/11/97
		FI 972655 A	19/06/97
		HU 77775 A	28/08/98
		IL 116460 D	00/00/00
		JP 10510829 T	20/10/98
		NO 972681 A	11/06/97
		PL 320856 A	10/11/97
		SE 9404469 D	00/00/00
		SK 81197 A	05/11/97
		ZA 9510754 A	24/06/96
		SE 9502452 D	00/00/00